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(54) **Low temperature process for preparing alpha-anomer enriched 2-deoxy-2, 2-difluoro-D-ribofuranosyl sulfonates.**

(57) A stereoselective process for preparing alpha-anomer enriched 2-deoxy-2,2-difluoro-D-ribofuranosyl sulfonates by contacting a lactol with an base in an inert solvent, adjusting the temperature and adding a sulfonating reagent.

EP 0 576 229 A1

This invention pertains to a low temperature process for making 2-deoxy-2,2-difluoro-D-ribofuranosyl-1-α sulfonates for use as intermediates in the preparation of anti-neoplastic and anti-viral agents.

Fluorine substitution has been investigated extensively in drug research and biochemistry as a means of enhancing the biological activity and increasing the chemical or metabolic stability of nucleosides. The replacement of a hydrogen by fluorine in a bioactive molecule is expected to cause minimal steric pertubations with respect to the molecule's mode of binding to receptors or enzymes and aid in overcoming the chemical and enzymatic instability problems of nucleosides. Difluorodeoxynucleosides are typically synthesized by coupling a 2-deoxy-2,2-difluoro-D-ribofuranosyl sulfonate with a purine or pyrimidine nucleobase.

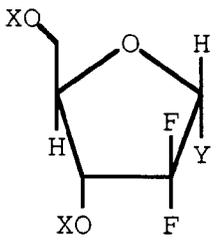
U.S. Patent 4,526,988 describes a process for making a hydroxy-protected 1-methanesulfonyl-2-deoxy-2, 2-difluoro-D-ribofuranosyl derivative by reacting 3,5-bis(t-butyldimethyl silyoxy) hydroxy protected 2-deoxy-2,2-difluoro-D-ribofuranose dissolved in dichloromethane with methanesulfonyl chloride, in an equimolar amount cf a suitable acid scavenger such as triethylamine for 3 hours at about 25°C. The resulting compound is coupled with a purine or pyrimidine base to form an anomeric mixture of nucleosides.

However, in order to stereoselectively prepare beta-anomer nucleosides via S_N2 displacement requires a process for preparing alpha-anomer enriched ribofuranosyl sulfonate intermediates for use in the nucleoside synthesis.

Accordingly, one object of the present invention is to provide a stereoselective process for preparing alpha-anomer enriched ribofuranosyl sulfonate intermediates.

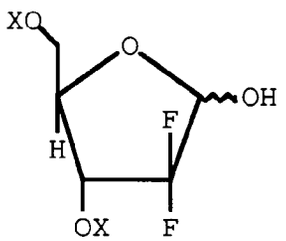
Another object of the present invention is to provide a stereoselective process for preparing alpha-anomer enriched ribofuranosyl sulfonates in high yields.

According to the present invention, there is provided a stereoselective low temperature process for preparing an alpha-anomer enriched ribofuranosyl derivative of the formula



(I);

wherein each X is independently selected from hydroxy protecting groups and Y is selected from the group consisting of alkylsulfonyloxy and substituted alkylsulfonyloxy comprising contacting a lactol of the formula



(II);

wherein X is as defined above; with a base in an inert solvent; adjusting the temperature; and adding a sulfonating reagent.

Throughout this document, all temperatures are in degrees Celsius, all proportions, percentages and the like, are in weight units and all mixtures are in volume units, except where otherwise indicated. Anomeric mixtures are expressed as a weight/weight ratio or as a percent. The term "xylenes" refers to all isomers of xylene and mixtures thereof. The term "lactol" alone or in combination refers to a 2-deoxy-2,2-difluoro-D-ribofuranose. The term "halo" alone or in combination refers to fluoro, chloro, bromo and iodo. The term "alkyl" alone or in combination refers to straight and branched chain aliphatic hydrocarbon groups which preferably contain up to 7 carbon atoms, such as, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, n-hexyl, 3-methylpentyl groups and the like or substituted straight and branched chain aliphatic hydrocarbons such as chloroethane, 1,2-dichloroethane, trifluoromethane and the like. The term "alkoxy" alone or in combination refers to compounds of the general formula AO; wherein A is an alkyl as defined above. The term "aryl" alone or in combination refers to phenyl and substituted derivatives thereof. The term "aromatic" alone or in combination refers to benzene-like structures containing (4n + 2) delocalized πelectrons. The terms "sulfonate" or "sulfonyloxy"

alone or in combination refer to compounds of the general formula BSO_3, wherein B is an alkyl or aryl group as defined above. The term "substituted" alone or in combination refers to the replacement of hydrogen or a common moiety by one or more of the groups selected from cyano, halo, carboalkoxy, toluoyl, nitro, alkoxy, alkyl, dialkylamino and electron-withdrawing groups such as a halo or nitro group. The phrase "anomer enriched" alone or in combination refers to an anomeric mixture wherein the ratio of a specified anomer is greater than 1:1 and includes substantially pure anomer.

The preparation of suitable lactol starting materials is described in U.S. Patent 4,965,374. The lactol is treated with a base in an inert solvent at room temperature.

Suitable bases are amines selected from the group consisting of trimethylamine, triethylamine (Et_3N) , tripropylamine, tributylamine, diisopropylethylamine, dimethylethylamine, diethylmethylamine, N-methylmorpholine, N,N-dimethylbenzylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, and mixtures thereof. The amine base preferably has a pKa from about 8 to about 20 and is employed in an equimolar amount relative to the amount of lactol used and more preferably from about 1.2 molar equivalents to about 2 molar equivalents.

The solvent employed preferably has a freezing point below about -78°C and is selected from the group consisting of toluene, acetone, dichloromethane, glyme, tetrahydrofuran, 1-nitropropane, 2-nitropropane, dichlorofluoromethane, nitroethane, chloroform, freon, and mixtures thereof; more preferred is dichloromethane.

The temperature of the mixture is then lowered to as low as a few degrees above the freezing point of the solvent selected; more preferably the temperature is lowered to a temperature below 0° more preferably to a temperature from about -40°C to about -120°C. While not wishing to be bound by theory it is believed that the low temperature shifts the alpha to beta ratio of the lactol in base in favor of the alpha-anomer in a range of from about 2:1 to about 4:1 alpha to beta. In support of this theory, a compound of formula II, where X is benzoyl, was dissolved in dichloromethane. After adding triethylamine and stirring at room temperature for 30 minutes, the temperature of the reaction mixture was lowered. An ^{19}F NMR analysis, taken at various temperatures, showed an increase in the alpha to beta ratio of the lactol as the temperature was lowered:

Temperature	Alpha/Beta Ratio
19°C	2.0:1
-3°C	2.3:1
-23°C	2.5:1
-43°C	3.0:1
-63°C	3.6:1
-83°C	4.4:1

The ionized lactol is trapped in solution at the low temperature and higher alpha-anomer ratio by adding a sulfonating reagent to the solvent mixture forming the alpha-anomer enriched ribofuranosyl derivatives of formula I.

The sulfonating reagent is selected from the group consisting of alkylsulfonyl halide, substituted alkylsulfonyl halide, alkylsulfonyl anhydride and substituted alkylsulfonyl anhydride. Preferred alkylsulfonyl halides are selected from the group consisting of methanesulfonyl halide, ethanesulfonyl halide, 2-chloroethanesulfonyl halide.

The hydroxy protecting groups (X) are known in the art and are described in Chapter 3 of Protective Groups in Organic Chemistry, McOmie Ed., Plenum Press, New York (1973), and Chapter 2 of Protective Groups in Organic Synthesis, Green, John, J. Wiley and Sons, New York (1981); preferred are ester forming groups such as formyl, acetyl, substituted acetyl, propionyl, butynyl, pivalamido, 2-chloroacetyl, benzoyl, substituted benzoyl, phenoxycarbonyl, methoxyacetyl; carbonate derivatives such as phenoxycarbonyl, t-butoxycarbonyl, ethoxycarbonyl, vinyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl and benzyloxycarbonyl; alkyl ether forming groups such as benzyl, diphenylmethyl, triphenylmethyl, t-butyl, methoxymethyl, tetrahydropyranyl, allyl, tetrahydrothienyl, 2-methoxyethoxy methyl; and silyl ether forming groups such as trialkylsilyl, trimethylsilyl, isopropyldialkylsilyl, alkyldiisopropylsilyl, triisopropylsilyl, t-butyldialkylsilyl and 1,1,3,3-tetraisopropyldisloxanyl; carbamates such as N-phenylcarbamate and N-imidazoylcarbamate; however more preferred are benzoyl, mono-substituted benzoyl and disubstituted benzoyl, acetyl, pivalamido, triphenylmethyl ethers, and silyl ether forming groups, especially t-butyldimethylsilyl; while most preferred is benzoyl.

In another aspect, the invention is a stereoselective process for preparing an alpha-anomer enriched ribofuranosyl derivative of formula I using bulky arylsulfonating reagents and a sulfonating catalyst. When substituted arylsulfonyl halide or substituted arylsulfonyl anhydride are used, a catalyst, such as 4-dimethylaminopyridine (DMAP), 4-pyrrolidinopyridine or mixtures thereof, must be used in conjunction with the sulfonating reagent. The sulfonating catalysts may be used alone, as an acid-scavenging agent or in combination with an amine base, such as triethylamine. Suitable sulfonating catalysts are for example 4-dimethylaminopyridine and 4-pyrrolidinopyridine. Preferred arylsulfonyl halides are selected from the group consisting of nitrobenzenesulfonyl halide, dinitrobenzenesulfonyl halide, bromobenzenesulfonyl halide and dibromobenzenesulfonyl halide.

The present process is preferably carried out under an inert atomosphere at atmospheric conditions and is substantially complete in about 30 minute to about 24 hours.

The progress of the present process may be followed using high pressure liquid chromotography (HPLC) or NMR spectroscopy.

The following examples illustrate specific aspects of the present invention and are not intended to limit the scope thereof in any respect and should not be so construed.

Example 1

Preparation of alpha-anomer enriched 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-di-O-benzoyl-1-methanesulfonate

To a solution of 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-dibenzoate (40 mg) in CD_2Cl_2 (0.5 ml) was added triethylamine (0.025 ml). After stirring at room temperature for 30 minutes the entire mixture was cooled to -78°C then methanesulfonyl chloride (0.01 ml) was added. The reaction temperature was maintained between -78°C and -80°C for 30 minutes then warmed to room temperature. HPLC analysis indicated that the reaction was complete. The anomeric ratio of the titled compound, as determined by ^{19}F NMR analysis, was 4:1 alpha to beta.

Example 2

Preparation of alpha-anomer 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-di-O-benzoyl-1-methanesulfonate

To a solution of 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-dibenzoate (60 g, 95% pure) in dichloromethane (600 ml) was added triethylamine (31.5 ml, 1.5 eq.). After stirring at room temperature for 30 minutes the mixture was cooled to -78°C. After 5 minutes, methanesulfonyl chloride (14 ml, 1.2 eq.) in dichloromethane (140 ml) was added to the mixture. The reaction temperature was maintained between -78°C and -80°C under nitrogen for one hour. HPLC analysis indicated that the reaction was complete. The anomeric ratio of the titled compound, as determined by HPLC analysis, was 3.53:1 alpha to beta.

To isolate the titled compound the reaction mixture was washed with water, 1 N HCl solution and 5% sodium bicarbonate solution (300 ml each). The organic layer was separated and dried over anhydrous magnesium sulfate. The titled compound (31.5 g) was obtained in a yield of 46 percent. mp 88-89°C; $[\alpha]_D$ (c 1.01, $CHCl_3$) +84.2°; $[\alpha]_{365nm}$ +302.0°; Elemental Analysis: $C_{20}H_{18}O_8SF_2$: (Calc.) C 52.63; H 3.98; F 8.33; S 7.02 (456.4) (Actual): C 52.92; H 3.82; F 8.33; S 7.30 ; ^1H NMR ($CDCl_3$): δ= 3.17 (CH_3), 4.66 and 4.76 (C-5H), 4.84 (C-4H), 5.57 (C-3H), 6.13 (C-1H); ^{13}C NMR ($CDCl_3$) : δ= 40.22 (CH_3), 62.51 (C-5H), 71.03 (C-3H; $J_{c,F}$ = 18.3, 38.5 Hz), 82.75 (C-4H), 99.59 (C-1H; $J_{c,F}$ = 25.5, 48.3 Hz), 122.24 (C-2H; $J_{c,F}$ = 259, 286 Hz).

Example 3

Preparation of alpha-anomer 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-di-O-benzoyl-1-methanesulfonate

To a solution of 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-dibenzoate (172 g, 95% pure,) in dichloromethane (1315 ml) was added triethylamine (69.1 g, 1.5 eq.). After stirring at room temperature for 30 minutes the mixture was cooled to -78°C. A separate solution of methanesulfonyl chloride (63.0 g, 1.2 eq.) in dichloromethane (504 ml) was cooled to -20°C and added under nitrogen over 3 to 5 minutes to maintain the temperature of the reaction mixture between -78°C and -85°C. The reaction mixture was stirred for 50 minutes then slowly warmed to 0°C. HPLC analysis indicated that the reaction was complete. The anomeric ratio of the titled compound, as determined by HPLC analysis, was 3.76:1 alpha to beta.

To isolate the titled compound, the reaction mixture was washed with 1N aqueous HCl solution, 5 percent sodium bicarbonate solution and water (600 ml) then dried over magnesium sulfate. The organic layer was

separated and dried under vacuum to give 152 g of the titled compound.

Example 4

Preparation of alpha-anomer enriched 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-di-O-benzoyl-1-(p-nitrobenzene) sulfonate

To a solution of 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-dibenzoate (100 mg), dichloromethane (1 ml) under nitrogen was added 4-dimethylaminopyridine (48 mg, 1.5 eq.). After stirring at room temperature for 30 minutes the mixture was cooled to -78°C then stirred for 15 minutes and treated with a solution of p-nitrobenzenesulfonyl chloride (78 mg, 0.317 mM, 1.2 eq.) in dichloromethane (1 ml).

To isolate the titled compound the reaction mixture was added to 1 N aqueous HCl. The organic layer was separated and washed with 5 percent sodium bicarbonate solution and water (1 ml) and dried over magnesium sulfate, filtered and concentrated to give a thick oil. An ^{19}F NMR analysis of the oil indicated that the anomeric ratio of the titled compound was 1.57:1 alpha to beta.

Example 5

Preparation of alpha-anomer enriched 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-dibenzoyl-1-(2,4-dinitro benzene)sulfonate

To a solution of 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-dibenzoate (100 mg) in dichloromethane (1 ml) under nitrogen was added 4-dimethylaminopyridine (48 mg, 1.5 eq.). After stirring at room temperature for 30 minutes the mixture was cooled to -78°C and stirred for 15 minutes then treated with a solution of 2,4-dinitrobenzenesulfonyl chloride (74.5 mg, 1.2 eq.) in dichloromethane (1 ml). Formation of the titled compound was verified by converting the 2,4-dinitrobenzenesulfonate to 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-di-O-benzoyl bromide. This was carried out by adding tetrabutylammonium bromide to the reaction mixture at -78°C immediately after adding the 2,4-dinitrobenzenesulfonyl chloride. An ^{19}F NMR analysis revealed that the alpha to beta ratio of the bromo anomer was 1:2.2. Since the bromination was a S_N2 displacement, the anomeric ratio of the titled compound was calculated to be 2.2:1 alpha to beta.

Example 6

Preparation of alpha-anomer 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-dibenzoyl-1-trifluoromethanesulfonate

To 1 g of 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-dibenzoate was added 10 ml of dichloromethane and 0.54 ml of triethylamine. This solution was stirred at 23°C for 30 minutes, cooled to -78°C and reacted with 0.57 ml of trifluoromethanesulfonyl anhydride, in 0.50 ml of dichloromethane, to form an alpha-anomer enriched 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-dibenzoyl-1-trifluoro-methanesulfonate intermediate in solution. Care was taken to maintain the temperature of the reaction mixture below -65°C. An ^{19}F nuclear magnetic resonance (NMR) analysis of the alpha-anomer enriched 2-deoxy-2,2-difluoro-D-ribo-furanosyl-3,5-dibenzoyl-1-trifluoromethanesulfonate intermediate at 65°C provided the following data:
^{19}F NMR (300 MHz, $CDCl_3$), δ-77 (s, 3F, CF3SO2-), -111 (d, J=257 Hz, 1F, alpha-anomer), -122 (d, J=242 Hz, 1F, beta-anomer), -124 (d, J=257 Hz, 1F, alpha-anomer), -126 ppm (d, J=242 Hz, 1F, beta-anomer). It should be noted that all ^{19}F NMR peak shifts are relative to hexafluorobenzene, which was assigned a frequency of -162.9 ppm. The ^{19}F NMR specturm also indicated fluorine - proton couplings however, the nature of these couplings were not determined.

The following Table shows the effects of the temperature and amine base on the anomeric ratio of the ribofuranosyl derivatives of formula I, prepared in accordance with the present process.

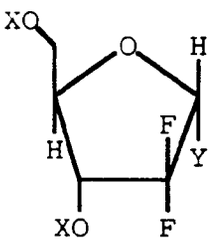
Table

Sulfonating Reagent	Base	Temperature	α:β Ratio (I)
p-nitrobenzenesulfonyl chloride	Et_3N	-78°C	1:7
p-nitrobenzenesulfonyl chloride	DMAP	-78°C	1:7
2,4-dinitrobenzenesulfonyl chloride	Et_3N	-78°C	1:2
2,4-dinitrobenzenesulfonyl chloride	DMAP	-78°C	2:1
Ethanesulfonyl chloride	Et_3N	23°C	1:1.5
Ethanesulfonyl chloride	Et_3N	-78°C	1.3:1
2-chloro-1-ethane sulfonyl chloride	Et_3N	23°C	1:1
2-chloro-1-ethane sulfonyl chloride	Et_3N	-78°C	2.7:1

The ribofuranosyl derivative of Formula (I) in the above Table is the corresponding 2-deoxy-2,2-difluoro-D-ribofuranosyl-3,5-di-O-benzoyl-1-alkyl or -aryl sulfonate.

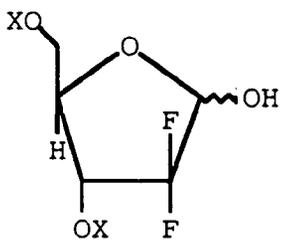
Claims

1. A stereoselective low temperature process for preparing an alpha-anomer enriched ribofuranosyl derivative of the formula



(I);

wherein each X is independently selected from hydroxy protecting groups and Y is selected from the group consisting of alkylsulfonyloxy, arylsulfonyloxy and substituted alkylsulfonyloxy or substituted arylsulfonyloxy; comprising contacting a lactol of the formula



(II);

wherein X is as defined above; with a base in an inert solvent; adjusting the temperature and adding a sulfonating reagent provided that when the sulfonating reagent provides a arylsulfonyloxy group a sulfonating catalyst is present.

2. The process of Claim 1 wherein the solvent is selected from the group consisting of toluene, acetone, dichloromethane, glyme, tetrahydrofuran, 1-nitropropane, 2-nitropropane, dichlorofluoromethane, nitroethane, chloroform, freon, and mixtures thereof.

3. The process of Claims 1 or 2 wherein the base is an amine selected from the group consisting of trimethylamine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dimethylethylamine, diethylmethylamine, N-methylmorpholine, N,N-dimethylbenzyl amine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, and mixtures thereof.

4. The process of Claims 1, 2 or 3 wherein the amount of amine base is from about 1 equivalent to about 2 equivalents.

5. The process of any one of the preceeding claims wherein the temperature is adjusted from about -40°C to about -120°C.

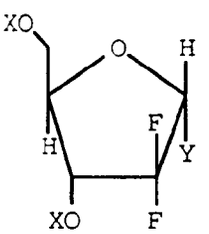
6. The process of any one of the preceeding claims wherein the sulfonating reagent is selected from the group consisting of alkylsulfonyl halide, substituted alkylsulfonyl halide, alkylsulfonyl anhydride, and substituted alkylsulfonyl anhydride.

7. The process of Claim 6 wherein the alkylsulfonyl halide is selected from the group consisting of methanesulfonyl chloride, 2-chloroethanesulfonyl chloride and ethanesulfonyl chloride.

8. The process of any one of the preceeding claims comprising adding a sulfonating reagent selected from the group consisting of substituted arylsulfonyl halides and substituted arylsulfonyl anhydrides and a sulfonating catalyst selected from 4-dimethylaminopyridine, 4-pyrrolidinopyridine, and mixtures thereof.

9. The process of Claim 8 wherein the substituted arylsulfonyl halide is selected from nitrobenzenesulfonyl chloride, dinitrobenzenesulfonyl chloride, bromobenzenesulfonyl chloride and dibromobenzenesulfonyl chloride and the sulfonating catalyst is N,N-dimethylaminopyridine.

10. An alpha-anomer enriched ribofuranosyl derivative of the formula



(I);

wherein each X is independently selected from hydroxy protecting groups and Y is selected from the group consisting of alkylsulfonyloxy, arylsulfonyloxy, substituted alkylsulfonyloxy and substituted alkylsulfonyloxy.

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EUROPEAN SEARCH REPORT

Application Number
EP 93 30 4818

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	SYNTHESIS no. 6, 1 June 1992, STUTTGART, GERMANY pages 565 - 570 CHOU, T. S. ET AL 'Stereospecific synthesis of 2-deoxy-2,2-difluororibonolactone and its use in the preparation of 2'-deoxy-2',2'-difluoro-beta-D-ribofuranosyl pyrimidine nucleosides: the key role of selective crystallization.' * page 566, column 1, line 10 - line 17 * * page 568, column 1, line 29 - line 42 * ---	1-4,6,7, 10	C07H11/00 C07H13/08
X	THE JOURNAL OF ORGANIC CHEMISTRY vol. 53, no. 11, 27 May 1988, WASHINGTON, D. C., UNITED STATES pages 2406 - 2409 HERTEL, L. W. ET AL 'Synthesis of e-deoxy-2,2-difluoro-D-ribose and 2-deoxy-2,2-difluoro-D-ribofuranosyl nucleosides' * page 2407, column 2, line 13 - line 39; figure III * * page 2409, column 1, line 25 - line 40 * ---	1-4,6,7, 10	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07H
A	EP-A-0 306 190 (ELI LILLY AND COMPANY) * the whole document * -----	1	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20 SEPTEMBER 1993	MORENO C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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